Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Genitourinary Malignancies

Clara Hwang, MD

Senior Staff Physician, Clinical Assistant Professor

Henry Ford Cancer Institute

AAEM American Academy of Emergency Medicine — Champion of the Emergency Physician

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

sitc Society for Immunotherapy of Cancer

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Disclosures

- Consulting Fees: Dendreon, TEMPUS, Sanofi/Genzyme
- Contracted Research: Merck, Exelixis, Bayer, AstraZeneca, Genentech, Dendreon and Bausch
- Ownership Interest (<5%): Johnson and Johnson
- I will be discussing non-FDA approved indications during my presentation.

Outline

- Renal cell carcinoma
  - Approved immunotherapies
  - Future directions
- Urothelial carcinoma
  - Approved immunotherapies
  - Future directions
- Prostate cancer
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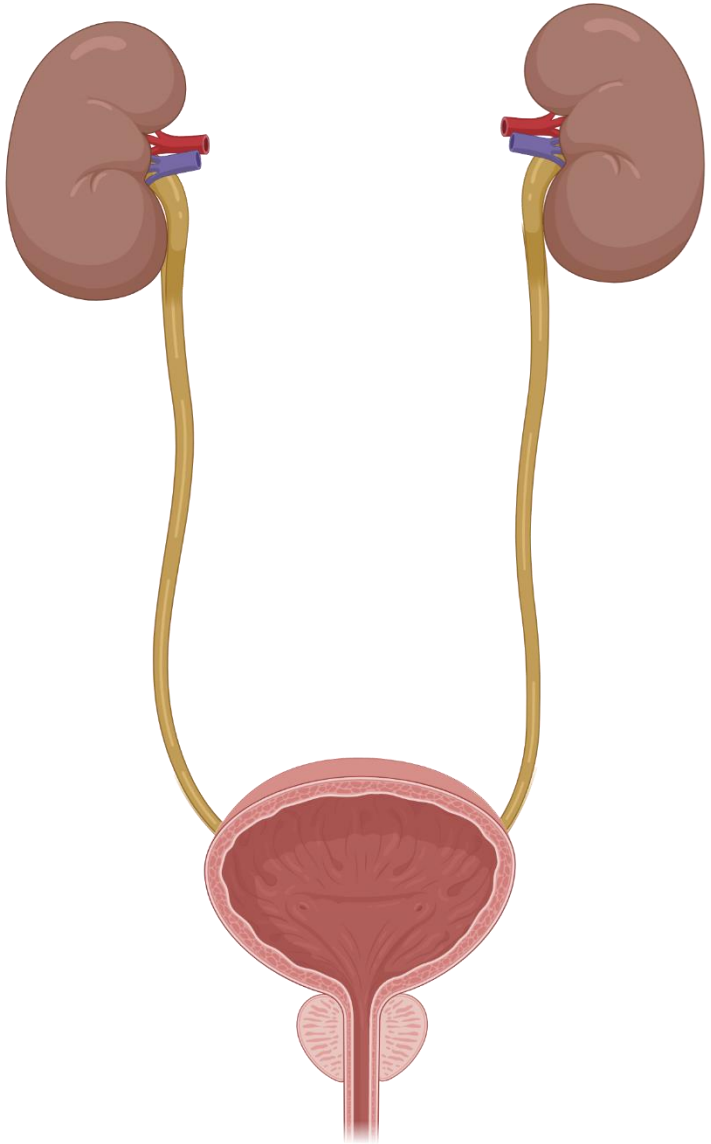
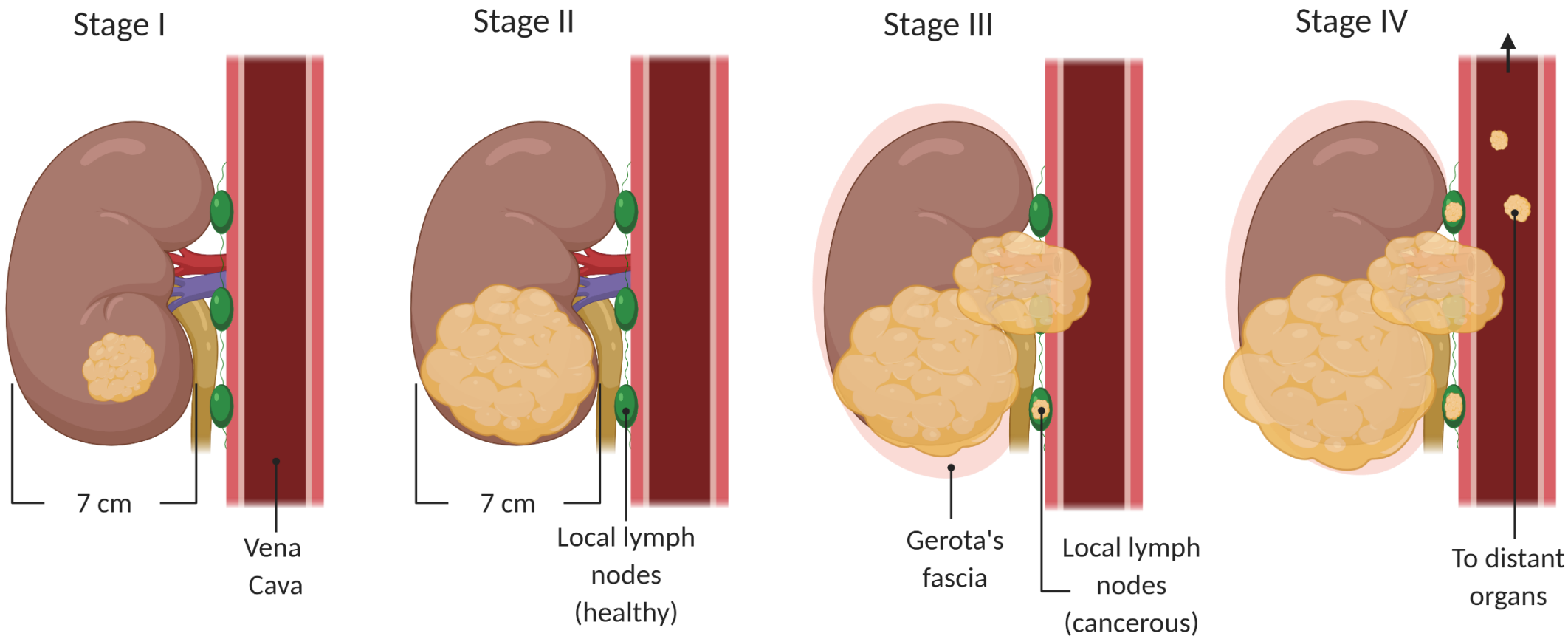


Renal cell carcinoma (RCC)



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FDA-approved immunotherapies for mRCC

Drug	Indication	Dose
High dose Interleukin-2	Metastatic RCC	600,000 International Units/kg (0.037 mg/kg) IV q8hr infused over 15 minutes for a maximum 14 doses, THEN 9 days of rest, followed by a maximum of 14 more doses (1 course)
Interferon-α + bevacizumab	Clear cell RCC	IFN 9 MIU s.c. three times a week + bevacizumab 10 mg/kg Q2W
Nivolumab	Clear cell RCC refractory to prior VEGF targeted therapy	240 mg Q2W or 480 mg Q4W
Nivolumab + ipilimumab	Clear cell RCC, treatment naïve	3 mg/kg nivo plus 1 mg/kg ipi Q3W x 4 doses then nivo maintenance at flat dosing
Pembrolizumab + axitinib	Advanced RCC, Treatment naïve	200 mg pembro Q3W or 400 mg Q6W + 5 mg axitinib twice daily
Avelumab + axitinib	Advanced RCC, Treatment naïve	800 mg avelumab Q2W + 5 mg axitinib twice daily
Nivolumab + cabozantinib	First-line advanced RCC	240 mg nivolumab Q2W or 480 mg Q4W + cabozantinib 40 mg daily

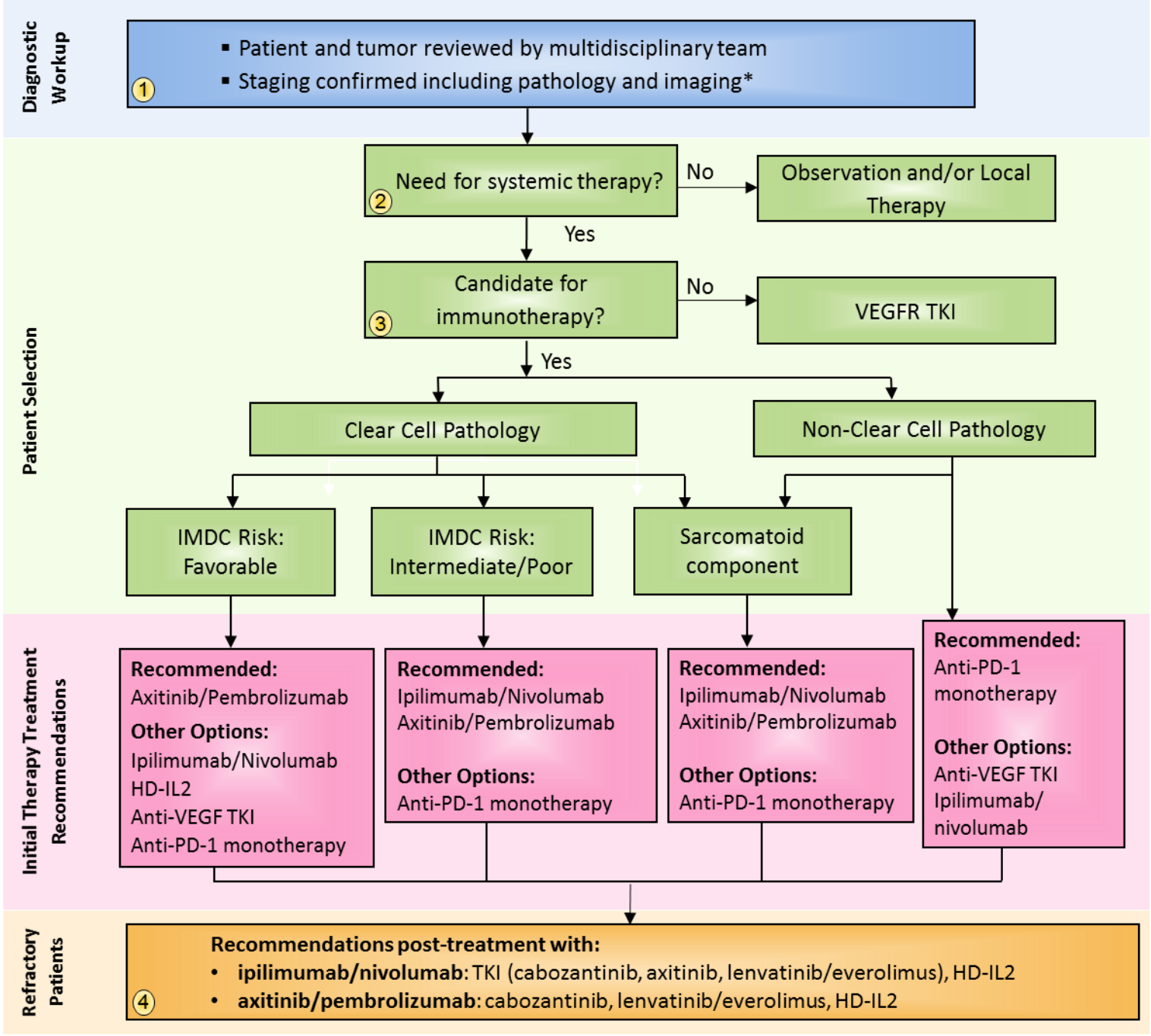
Front-line immunotherapy treatments for RCC

Study	Treatment arm(s)	Patient selection criteria	N	ORR	Median PFS (months)	Median OS (months)
CheckMate 214	Nivolumab + ipilimumab*	Untreated, advanced clear cell RCC (poor/intermediate risk)	550	42%	12.0	47.0
	Sunitinib		546	26%	8.3	26.6
KEYNOTE-426	Pembrolizumab + axitinb*	Untreated, advanced clear cell RCC	432	60%	15.4	NR
	Sunitinib		429	40%	11.1	35.7
JAVELIN Renal 101	Avelumab + axitinib*	Untreated, advanced clear cell RCC	442	52.5%	ITT: 13.3 PD-L1+: 13.8	ITT: NE PD-L1+: NE
	Sunitinib		444	27.3%	ITT: 8.0 PD-L1+: 7.0	ITT: NE PD-L1+: 25.6
IMmotion151	Atezolizumab + bevacizumab	Untreated, advanced clear cell or sarcomatoid RCC	454	ITT: 37% PD-L1+: 43%	ITT: 11.2 PD-L1+: 11.2	ITT: 33.6 PD-L1+: 34.0
	Sunitinib		461	ITT: 33% PD-L1+: 35%	ITT: 8.4 PD-L1+: 7.7	ITT: 34.9 PD-L1+: 32.7

*FDA-approved IO regimen

Tannir, ASCO-GU 2020; Pilmack, ASCO 2020; Choueiri, Ann Oncol 2020; Rini, Lancet 2019.

SITC Cancer Immunotherapy Guideline for advanced renal cell carcinoma



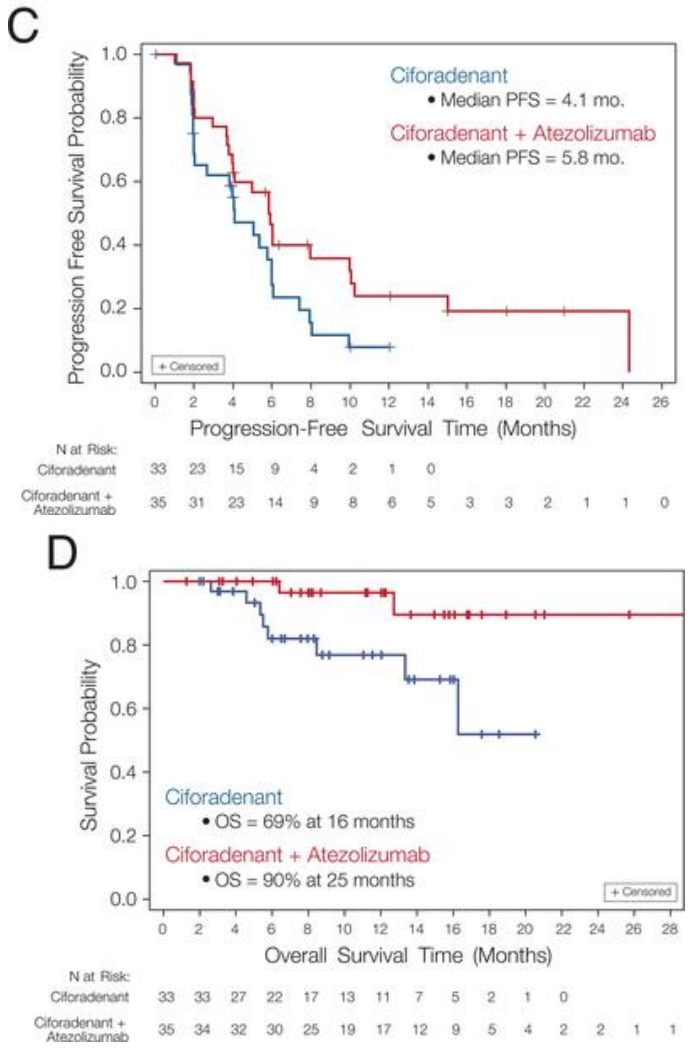
*Baseline imaging recommendations discussed in figure legend.

Notes: 1) Clinical Trials are always an option for any patient, in any category. 2) This recommendation may change as data matures.

Rini, J Immunother Cancer 2019.

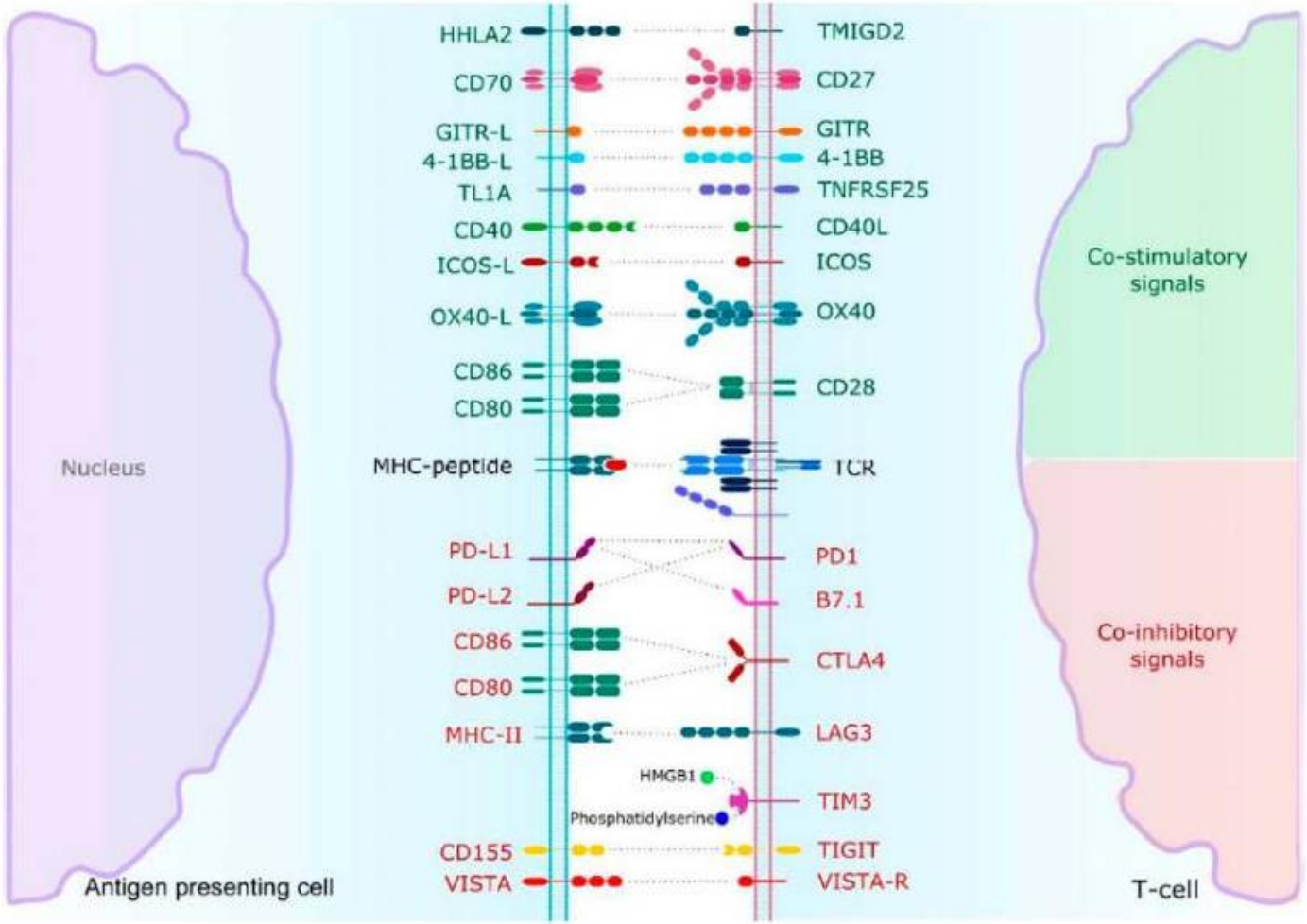
In development: A2AR antagonist + anti-PD-L1

Treatment arm	N	ORR	6-month disease control
Ciforadenant	33	3%	Naïve: 0%
			Prior ICI: 25%
Ciforadenant + atezolizumab	35	11%	Naïve: 50%
			Prior ICI: 35%



Fong, Ca Discov 2020

In development: additional immunotherapy approaches



Deleuze, Int J Mol Sci 2020

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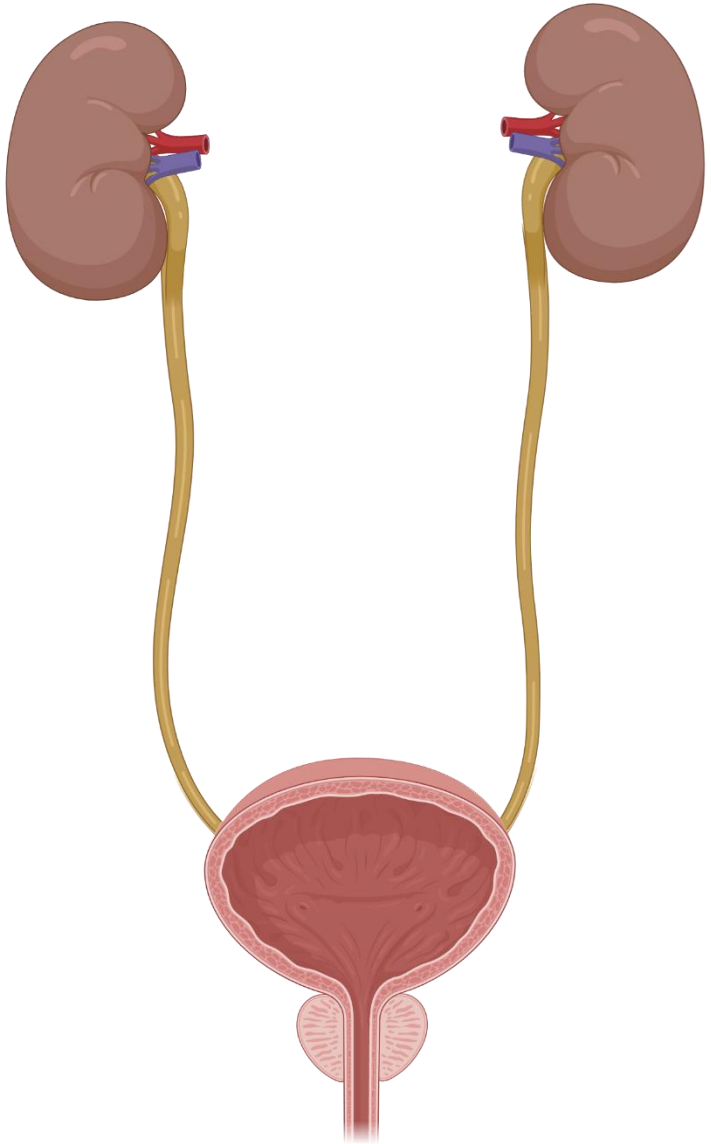
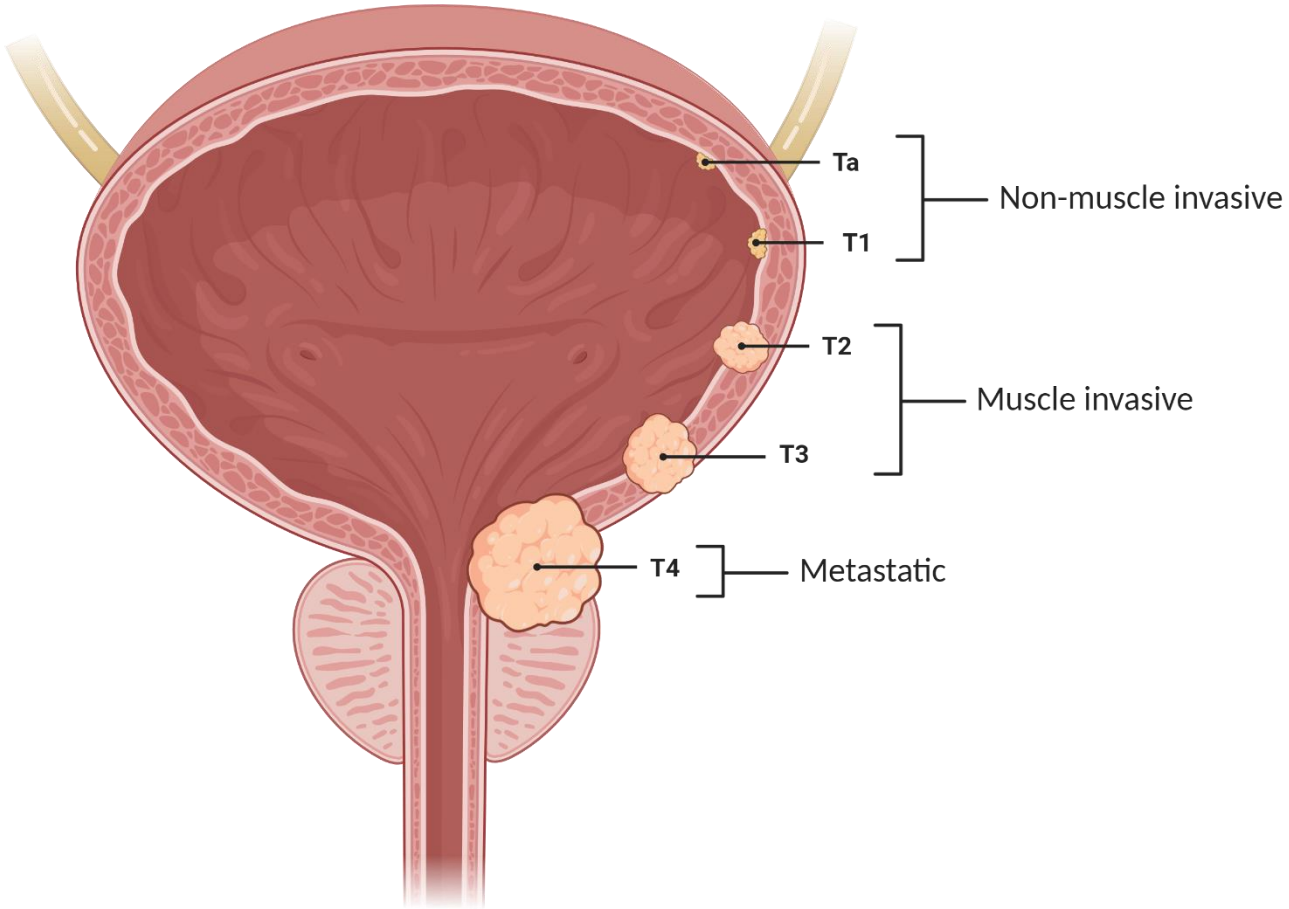


Urothelial carcinoma (UC)



Approved checkpoint inhibitor for non-muscle invasive bladder cancer

Drug	Indication	Dose
Pembrolizumab	BCG-unresponsive, high-risk NMIBC, with or without papillary tumors and ineligible for cystectomy	200 mg Q3W or 400 mg Q6W

Response, n (%)	KEYNOTE-057 cohort A (n=97)
Complete response	40 (41.2)
Non-complete response	56 (57.7)
Persistent	40 (41.2)
Recurrent	6 (6.2)
NMIBC stage progression	9 (9.3)
Progression to T2	0
Extravesical disease	1 (1.0)
Non-evaluable	1 (1.0)

FDA Advisory Committee Briefing Document, 2019.

Approved checkpoint inhibitors for mUC – *cisplatin refractory*

Drug	Indication	Dose
Avelumab	Advanced/metastatic UC	10 mg/kg Q2W
Nivolumab	Advanced/metastatic UC	240 mg Q2W or 480 mg Q4W
Pembrolizumab	Advanced/metastatic UC	200 mg Q3W or 400 mg Q6W

Approved checkpoint inhibitors for mUC – *cisplatin ineligible*

Drug	Indication	Dose
Atezolizumab	Advanced/metastatic UC (PD-L1 ≥5%)	1200 mg Q3W
Pembrolizumab	Advanced/metastatic UC (PD-L1 CPS ≥10)	200 mg Q3W or 400 mg Q6W

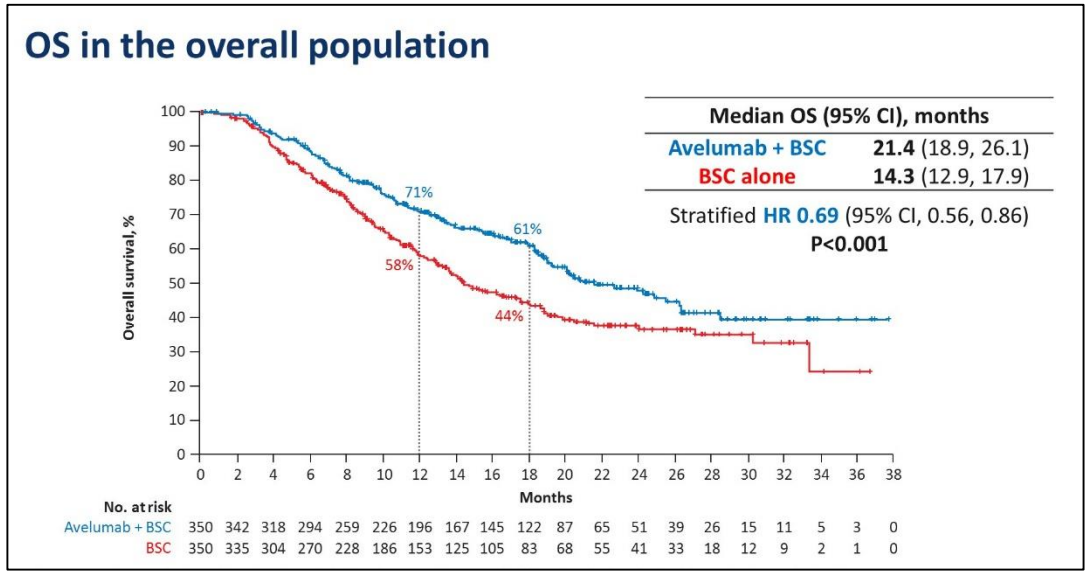
June 2018

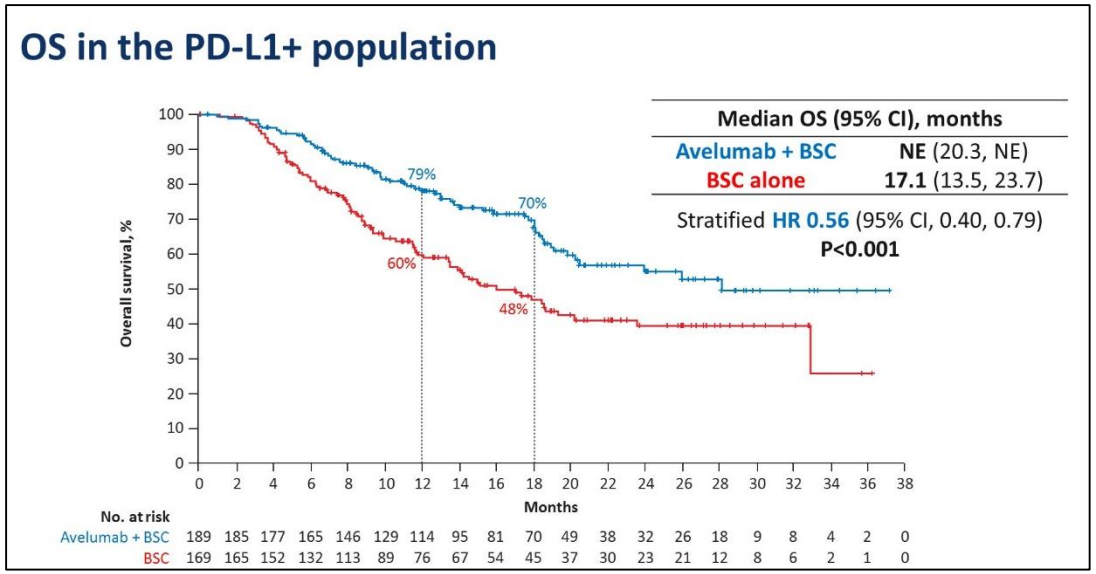
FDA limits the use of atezolizumab and pembrolizumab for some urothelial cancer patients

- Locally advanced or metastatic urothelial carcinoma and ineligible for cisplatin-based chemo and with detectable PD-L1 expression in tumor (CPS ≥ 10, pembro; IC ≥ 5% tumor area, atezo)
- Patients ineligible for any platinum-containing chemotherapy regardless of PD-L1 status

Approved checkpoint inhibitor for maintenance treatment

Drug	Indication	Dose
Avelumab	Maintenance of locally advanced/metastatic UC without progression on first-line Pt chemotherapy	800 mg Q2W



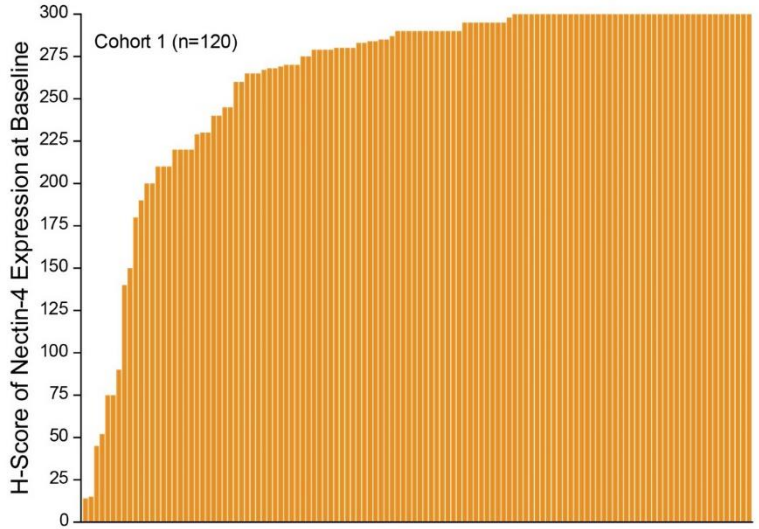


Powles, ASCO 2020.

Approved antibody-drug conjugate for mUC

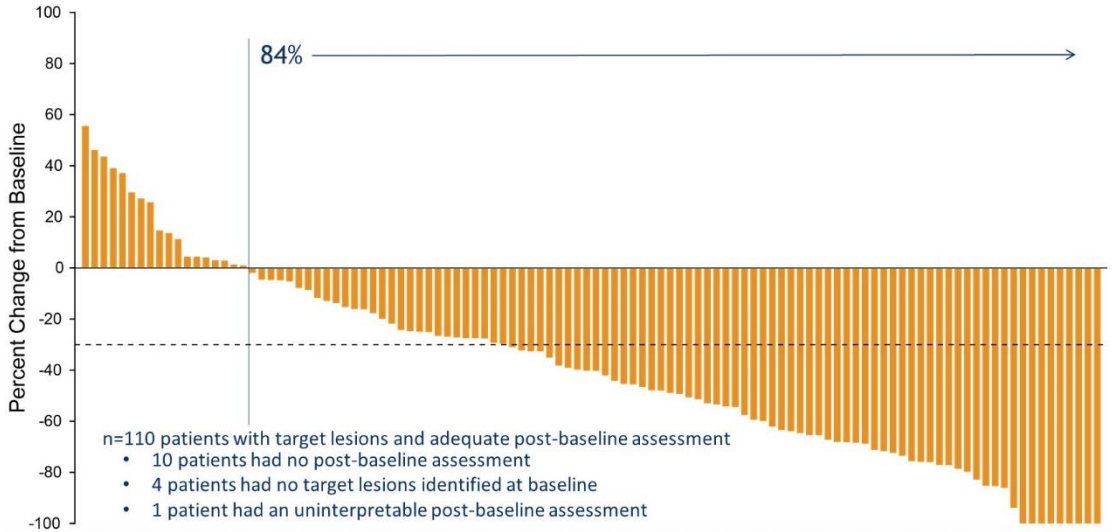
Drug	Indication	Dose
Enfortumab vedotin	Locally advanced/metatstatic UC with **previous αPD-1/PD-L1** and Pt-based chemotherapy	1.25 mg/kg IV on days 1, 8, and 15 of each 28-day cycle

EV-201: Cohort 1 Nectin-4 Expression



[1] Five patients did not have adequate tissue for Nectin-4 testing

EV-201: Cohort 1 Change in Tumor Measurements per BICR



Petrylak, ASCO 2019.

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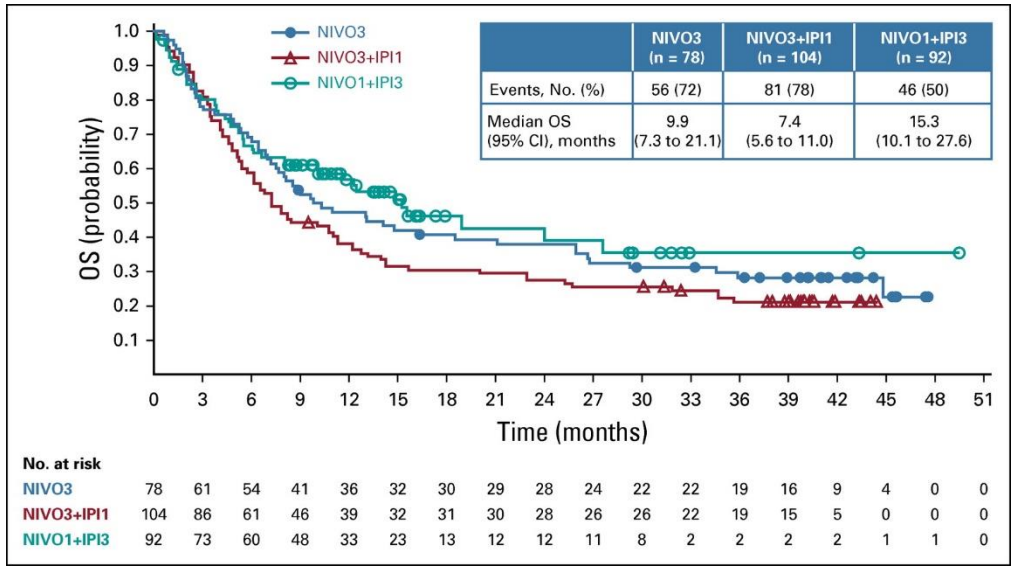
In development: Ipilimumab + Nivolumab CheckMate 032

Treatment arm	n	ORR	Median PFS	Median OS	Grade 3-4 TRAEs
Nivolumab 3 mg/kg Q3W	78	ITT: 25.6% PD-L1+: 26.9%	2.8 months	9.9 months	26.9%
Nivolumab 3 mg/kg + ipilimumab 1 mg/kg	104	ITT: 26.9% PD-L1+: 35.5%	2.6 months	7.4 months	30.8%
Nivolumab 1 mg/kg + ipilimumb 3 mg/kg	92	ITT: 38.0% PD-L1+: 58.1%	4.9 months	15.3 months	39.1%

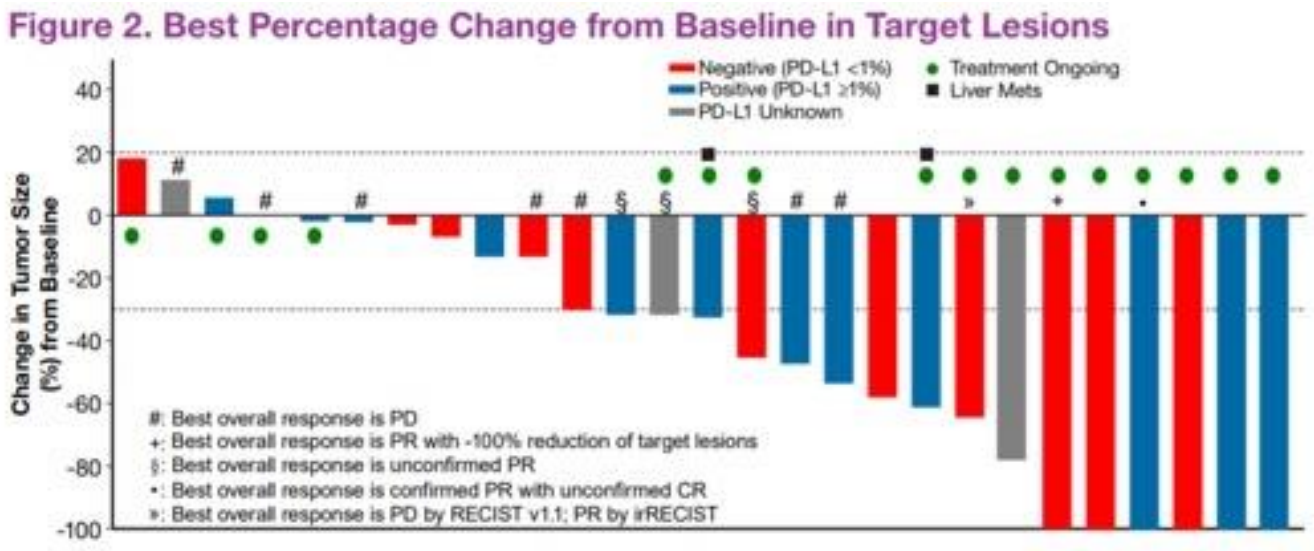


Sharma, J Clin Oncol 2019.

In development: NKTR-214 + nivolumab

Treatment	n	ORR
NKTR-214 + nivolumab	27	48%

After treatment, 70% of patients with PD-L1-negative tumors converted to PD-L1-positive.



Siefker-Radtke, ASCO-GU 2020.

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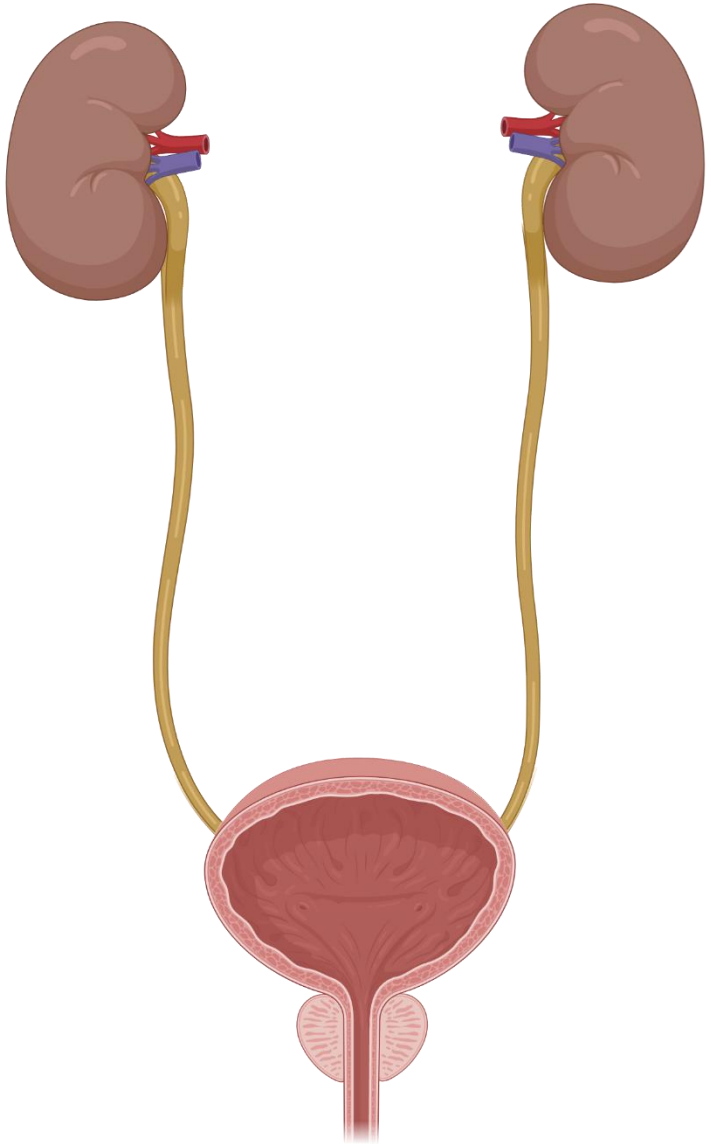
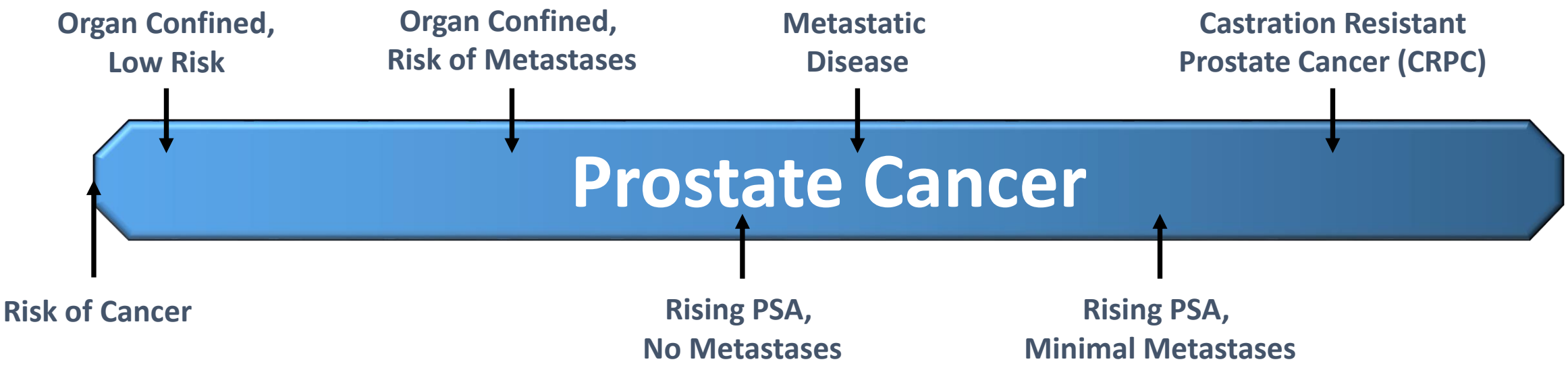
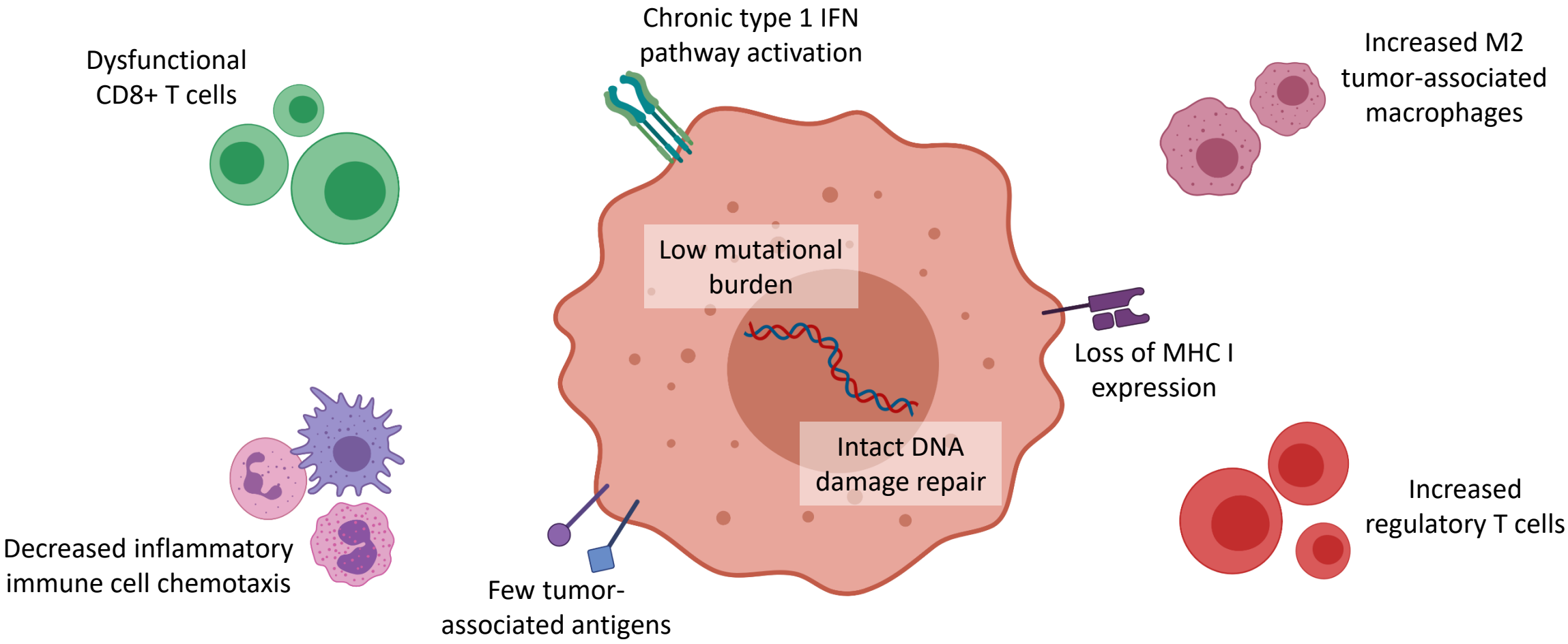


The Spectrum of Prostate Cancer



Immunology of prostate cancer



Vitkin, Front Immunol 2019.

Immunotherapy landscape in prostate cancer

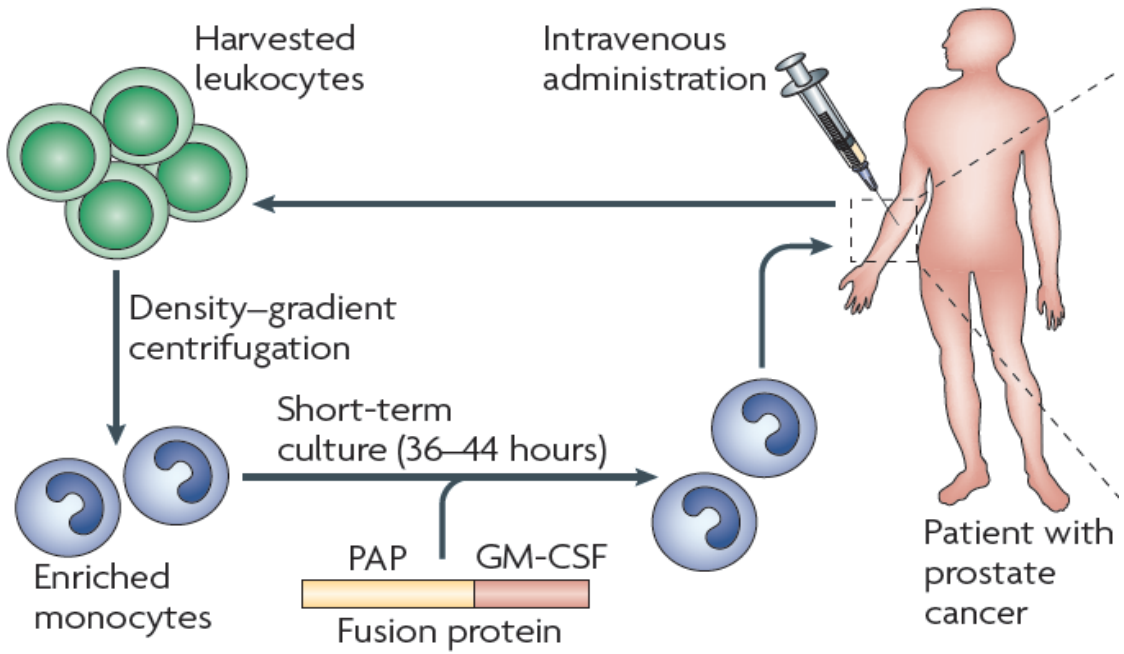
Trial	Treatment	Population	Key results
KEYNOTE-199	Pembrolizumab	RECIST-measurable PD-L1+ mCRPC	ORR: 5%
		RECIST-measurable PD-L1- mCRPC	ORR: 3%
		RECIST nonmeasurable mCRPC	DCR: 37%
KEYNOTE-365	Pembrolizumab + enzalutamide	Progression on previous hormonal and chemotherapies	PSA response rate: 21.8% Median OS: 20.4 months
	Pembrolizumab + olaparib		PSA response rate: 13% Median OS: 14 months
IMbassador250	Atezolizumab + enzalutamide	Progression on previous hormonal and chemotherapies	Median OS: 15.2 vs 16.6 months
	Enzalutamide		

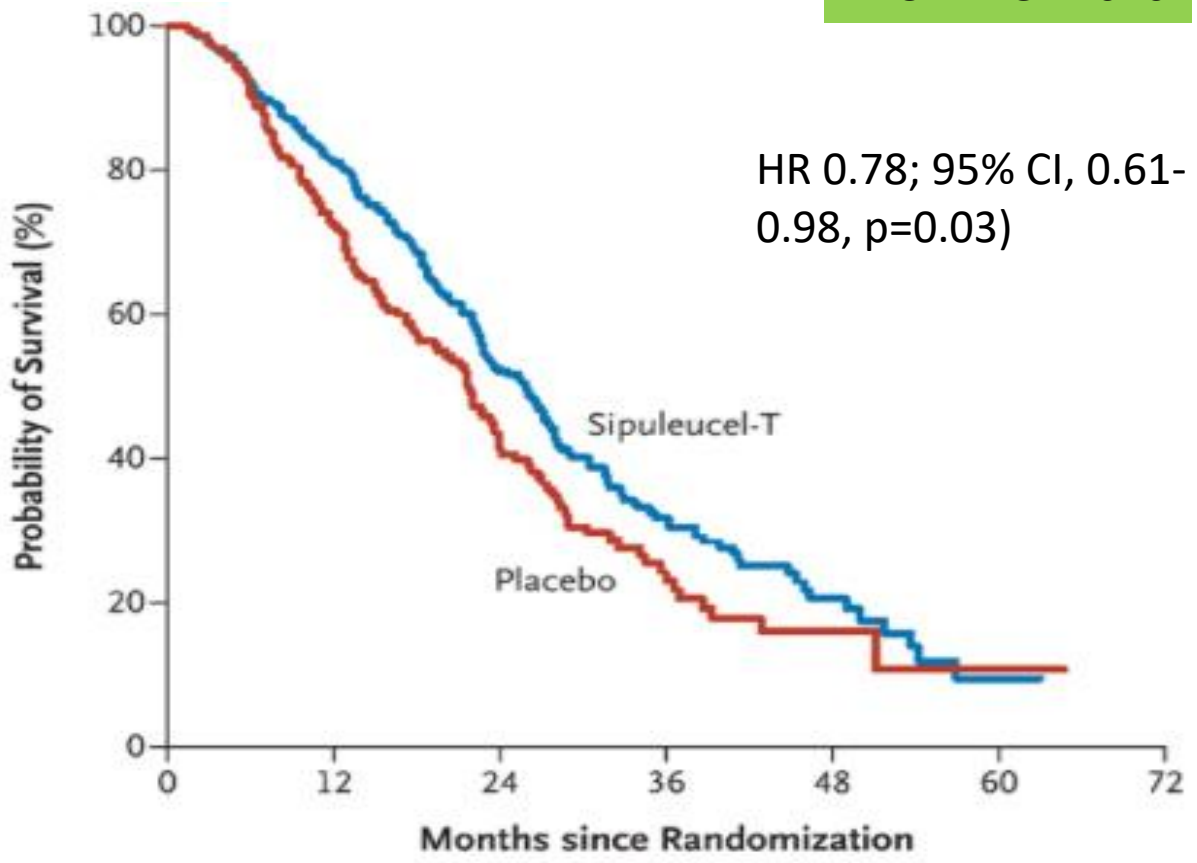
De Bono, ASCO 2018; Yu, AUA 2020; Sweeney, AACR 2020.

Sipuleucel-T in mCRPC

PROVENGE 2010

First anti-cancer therapeutic vaccine

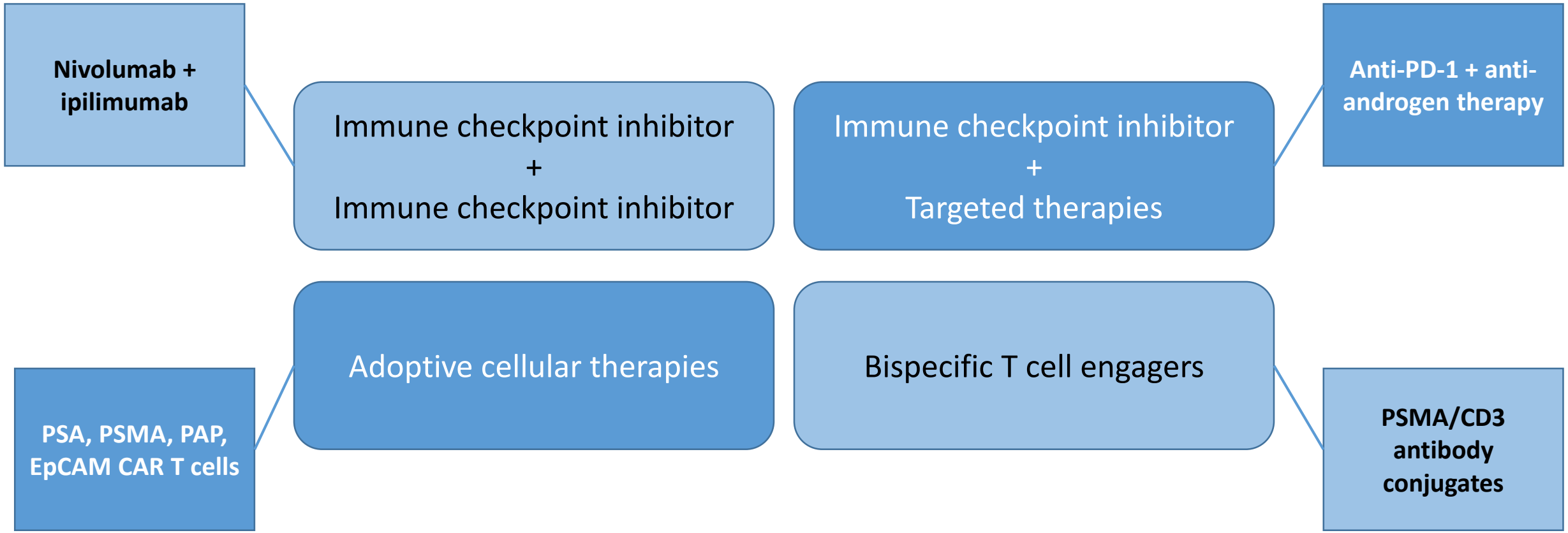




HR 0.78; 95% CI, 0.61-0.98, p=0.03)

Drake et al. Curr Opin Urol 2010
Kantoff et al. NEJM 2010

Future directions for prostate cancer immunotherapy



In development: nivolumab + ipilimumab in mCRPC

Trial	Treatment	Population	ORR	Median OS
CheckMate 650	Nivolumab + ipilimumab, then nivolumab maintenance	Progression on hormonal therapy, no chemotherapy	25%	19 months
		Progression on chemotherapy	10%	15.2 months

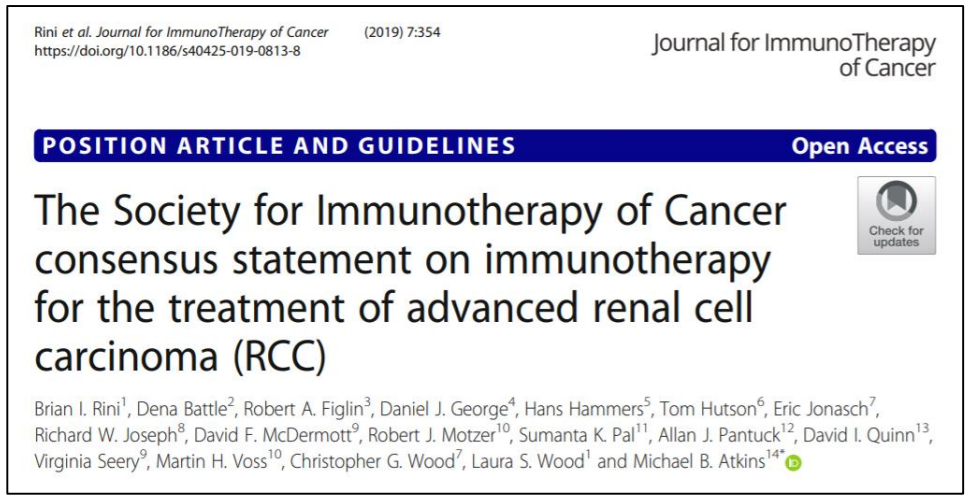
- Higher ORR in:
  - PD-L1 > 1%
  - DNA damage repair deficient
  - homologous recombination deficiency
  - high tumor mutational burden

Sharma, GU Cancer Symp 2019.

Conclusions

- The role of immunotherapy in GU malignancies is increasing
- In RCC, many front-line checkpoint inhibitor options are approved
- Multiple checkpoint inhibitors approved for advanced/metastatic urothelial carcinoma, as well as other settings in UC
- Low immune engagement in prostate cancer has limited the application of immunotherapy in this disease

Additional Resources



Rini *et al. Journal for ImmunoTherapy of Cancer* (2019) 7:354
https://doi.org/10.1186/s40425-019-0813-8

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES — Open Access

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of advanced renal cell carcinoma (RCC)

Brian I. Rini[1], Dena Battle[2], Robert A. Figlin[3], Daniel J. George[4], Hans Hammers[5], Tom Hutson[6], Eric Jonasch[7], Richard W. Joseph[8], David F. McDermott[9], Robert J. Motzer[10], Sumanta K. Pal[11], Allan J. Pantuck[12], David I. Quinn[13], Virginia Seery[9], Martin H. Voss[10], Christopher G. Wood[7], Laura S. Wood[1] and Michael B. Atkins[14*]

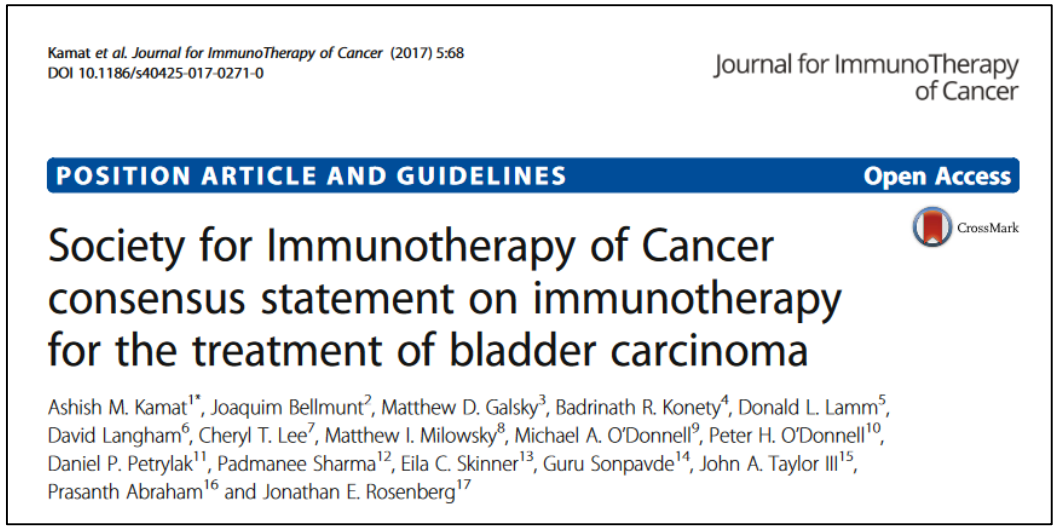
McNeel *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:92
DOI 10.1186/s40425-016-0198-x

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES — Open Access

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of prostate carcinoma

Douglas G. McNeel[1], Neil H. Bander[2], Tomasz M. Beer[3], Charles G. Drake[4], Lawrence Fong[5], Stacey Harrelson[6], Philip W. Kantoff[7], Ravi A. Madan[8], William K. Oh[9], David J. Peace[10], Daniel P. Petrylak[11], Hank Porterfield[12], Oliver Sartor[13], Neal D. Shore[6], Susan F. Slovin[7], Mark N. Stein[14], Johannes Vieweg[15] and James L. Gulley[16*]



Kamat *et al. Journal for ImmunoTherapy of Cancer* (2017) 5:68
DOI 10.1186/s40425-017-0271-0

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES — Open Access

Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of bladder carcinoma

Ashish M. Kamat[1*], Joaquim Bellmunt[2], Matthew D. Galsky[3], Badrinath R. Konety[4], Donald L. Lamm[5], David Langham[6], Cheryl T. Lee[7], Matthew I. Milowsky[8], Michael A. O'Donnell[9], Peter H. O'Donnell[10], Daniel P. Petrylak[11], Padmanee Sharma[12], Eila C. Skinner[13], Guru Sonpavde[14], John A. Taylor III[15], Prasanth Abraham[16] and Jonathan E. Rosenberg[17]

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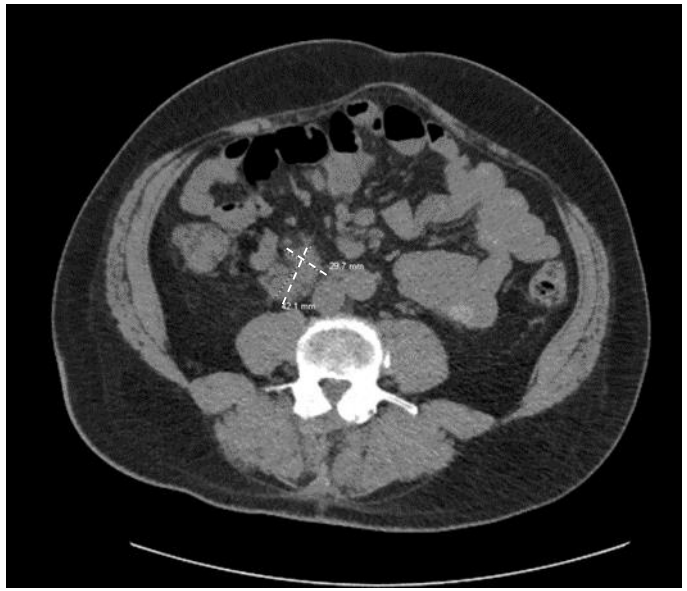
Acknowledgements

- Some figures created using biorender.com

Case Studies

Case Study 1

Mr. JR is a 68 yo male evaluated in clinic for metastatic castration-resistant prostate cancer. He developed biochemical recurrence six years ago after prostatectomy (pT3bN0, Gleason 4+4) and salvage radiation. He later developed castration-resistant metastatic disease. He has been treated with docetaxel, enzalutamide, and sipuleucel-T. His PSA is currently 31.8 ng/mL, alk phos 116, WBC 6.9, Hgb 10.5, Plt 306. Imaging with supraclavicular adenopathy (2.3cm), abdominopelvic adenopathy (largest 3cm), serosal metastasis between sigmoid colon and urinary bladder (4.4 cm). There are no bone metastases. Family history significant for mother with breast and uterine cancer; sister with gastric cancer, brother with colon cancer, and niece with uterine cancer.



Question for Case Study 1

What would you do next in management of this patient?

A. Cabazitaxel
B. Mitoxantrone
C. Apalutamide
D. Radium
E. Order further diagnostic testing

Question for Case Study 1

What would you do next in management of this patient?

A. Cabazitaxel – reasonable choice
B. Mitoxantrone – although symptom palliation was proven with mitoxantrone, less preferred because no survival benefit
C. Apalutamide – currently no indication in mCRPC
D. Radium - inappropriate in absence of bone metastases
E. Order further diagnostic testing – this choice was selected

Case Study 1

- Patient was sent for genetic testing and germline mutation in MLH1 was identified.

Tumor mutations in MLH1 and other DNA mismatch repair genes (MSH2, MSH6, PMS2) may result in microsatellite instability (MSI) due to deficient mismatch repair (dMMR).

Pembrolizumab was initiated based on approval for MSI-high/dMMR malignancies. He has completed nearly two years of therapy and PSA is currently undetectable.

Case Study 2

- Mr. JE is an 82 yo male who underwent left radical nephrectomy 9 months prior to initial evalution, pT3aN0, grade 2, ccRCC. He is referred because surveillance imaging with new sclerotic bone lesions; bone scan confirms uptake in R humerus, L scapula, ribs, spine, pelvis. IMDC intermediate risk (normal hemoglobin, calcium, neutrophil count, platelets and KPS 90%). History notable for type II diabetes, hypertension, kidney stones, and recurrent episodes of diverticulitis.

Question for Case Study 2

- How would you treat this patient?

- A. Pembrolizumab/ axitinib
- B. Cabozantinib
- C. High-dose IL-2
- D. Ipilimumab/ nivolumab
- E. Interferon-α + bevacizumab

Question for Case Study 2

- Multiple frontline treatment options are available for patients with metastatic renal cell carcinoma. Given the history of recurrent diverticulitis, this patient may be at higher risk of GI perforation with anti-angiogenesis therapies such as axitinib and cabozantinib. Ipilimumab/ nivolumab is approved in the frontline for patients with intermediate and poor risk ccRCC and is an attractive alternative for patients who have no history of auto-immune disease. High dose IL-2 and interferon-α are more toxic than immune checkpoint inhibitors without offering greater therapeutic benefits compared to newer immune therapies. The patient was treated with ipilimumab and nivolumab and did not progress for two years.
- A. Pembrolizumab/ axitinib
- B. Cabozantinib
- C. High-dose IL-2
- D. Ipilimumab/ nivolumab
- E. Interferon-α + bevacizumab